SIDE EFFECTS OF DRUGS

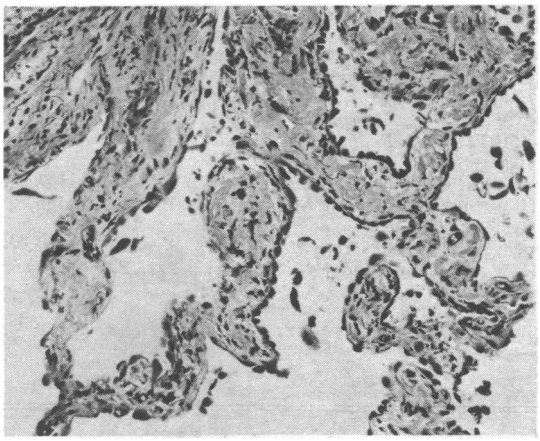
Interstitial lung disease in a patient treated with 5-fluorouracil and mitomycin C

Many cytotoxic agents are associated with pulmonary toxicity, the most common being bleomycin, methotrexate, and busulphan.[1] This complication, however, has not been recorded during treatment with 5-fluorouracil and mitomycin C. We report a case of interstitial lung disease occurring during treatment with these two agents.

Case report

A 55-year-old Caucasian man with a history of thyrotoxicosis treated with carbimazole was admitted to hospital in January 1976 with epigastric pain and weight loss. Laparotomy disclosed an antral carcinoma of the stomach with extensive lymph node disease, and local resection was carried out. Histological examination confirmed a well-differentiated adenocarcinoma with mestastases in lymph nodes. His postoperative course was uneventful and a chest radiograph was normal. In March he began nine weekly injections of 1 g fluorouracil, which were well tolerated. In January 1977 he began a further course of chemotherapy, 10 mg mitomycin C and 1 g fluorouracil being given intravenously every three weeks. After 12 treatments he developed breathlessness on exertion. Haemoglobin was 9·9 g/dl, and despite transfusion his breathlessness continued. In October chest radiography showed interstitial shadowing, but there was no history of factors known to be associated with interstitial lung disease.

Investigations—There was clubbing of the fingers but no clinical evidence of recurrent malignant disease. Haemoglobin was 10·4 g/dl, and erythrocyte sedimentation rate 100 mm in first hour. Liver function values and carcinoembryonic antigen titre remained normal. Sputum cytology was negative. Tests for antinuclear factor, rheumatoid factor, avian antigens, cryptococcal antigens, and aspergillus titre all gave negative results. Pulmonary function was normal except for a low transfer factor for carbon monoxide. The alveolar-arterial oxygen tension gradient was 5·99 kPa (45 mm Hg) (predicted value 2·21 ± SD 0·75 kPa; 16·6 ± 5·6 mm Hg[2]), and arterial oxygen and carbon dioxide tensions were low (Pao_2 8·7 kPa (65·4 mm Hg); $Paco_2$ 4·2 kPa (31·6 mm Hg)). Multiple transbronchial lung biopsies showed interstitial fibrosis with proliferation of the alveolar lining cells (figure).



Section of lung biopsy specimen showing interstitial lung disease, with thickening of alveolar walls and proliferation of alveolar lining cells. (Haematoxylin and eosin. ×52.)

Comment

5-Fluorouracil is an antimitotic agent that has been widely used. Despite this it has not been implicated as a cause of pulmonary fibrosis. In contrast, mitomycin C is a recently introduced cytotoxic antibiotic isolated from *Streptomyces caespitosus*. It is similar to bleomycin, which causes pulmonary fibrosis in 3-6% of all patients[3] and in 55% of patients given over 283 mg.[4] Cytotoxic agents used in combination may act synergistically to produce pulmonary toxicity.[5]

Results of investigations in our patient were consistent with, though not diagnostic of, fibrosing alveolitis. After stopping cytotoxic treatment he remained well, although a slight further reduction in Pao_2 and transfer factor for carbon monoxide occurred. Many patients in a multicentre gastric chemotherapy trial are receiving both fluorouracil and mitomycin C in large cumulative doses. It is therefore important to clarify this association, and we are undertaking a prospective study of all patients receiving mitomycin C and fluorouracil in this trial. Physicians should be aware of the possible association between interstitial lung disease and this cytotoxic regimen.

We thank Dr D Stableforth for help in performing the lung biopsy, Dr C Edwards for help with the histology and photograph, and Miss J Smith for help in preparing the manuscript.

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Pneumothorax after acupuncture

Acupuncture is in vogue as a therapeutic measure for various conditions. With increased use complications have also become more common. We describe three cases of pneumothorax that occurred after acupuncture.

Case reports

Case 1—A 74-year-old widow went to a non-medical therapist seeking relief from chronic arthritic pain and persistent malaise after a bout of pneumonia. She received five separate treatments. During each of these two needles were inserted immediately above the clavicles, and 18 needles were inserted into the knees. In the 24 hours after the last treatment she developed increasing breathlessness and attended the casualty department. A posteroanterior radiograph showed bilateral pneumothorax with about 25% collapse of the right lung and 40% collapse of the left, with associated widespread surgical emphysema of the left side. The left pneumothorax was treated with an intercostal catheter and underwater seal drainage. The right pneumothorax resolved without treatment and she made a full recovery.

Case 2—A 49-year-old shopkeeper attended an acupuncturist for relief from chronic tension arising from his job and marriage; tranquillisers prescribed by his doctor had been of no avail. Initial treatment was needles inserted into the neck, resulting in transient relief. His symptoms returned 24 hours later and he again consulted the therapist. He was treated with insertion of a further two sets of needles, the first into the anterior chest below the medial ends of the clavicles and the third and fifth intercostal spaces parasternally on both sides, and the second posteriorly over the scapula and lateral to the fourth, fifth, and sixth thoracic vertebrae over both lungs. After insertion of the needles into his back he suddenly became nauseated and giddy and the needles were immediately removed. Over the next 12 hours he developed severe pleuritic pain and came to the casualty department. Posteroanterior radiography showed a small pneumothorax at the apex of the left lung. Next day radiography showed the pneumothorax to have increased to about 30% collapse together with about 25% collapse of the right lung. Both pneumothoraces were treated with intercostal drainage and he made a full recovery.

Case 3—An 18-year-old clerk consulted an acupuncturist for treatment of asthma, which she had had since the age of 3. Needles were inserted into

the anterior chest and she developed pleuritic pain. The symptoms worsened overnight, and next day she came to the casualty department. Clinical examination suggested a right pneumothorax, and radiography confirmed about 30% collapse on that side. An intercostal catheter was inserted and she made a full recovery.

Comment

Acupuncture is generally undertaken with fine solid needles. In these cases 27-32-gauge needles were used, in keeping with the recommendation of 30-gauge needles not longer than 4 cm.[1] They are usually inserted with a twirling motion at an angle of 30-60° and stimulated electrically or manually.

Unilateral pneumothorax has been reported after acupuncture to the chest[2 3] and shoulder.[4] Procedures such as pleural aspiration and regional anaesthesia may also cause pneumothorax; in brachial plexus block, for example, the reported incidence is 0·5-4%.[5] There are two ways in which pneumothorax may develop after acupuncture to the chest. Perforation of the pleura may allow an inflow through the fistulous needle track, or the needle may puncture the lung. Entry of air through a small needle track may be slow. Delayed pneumothorax is a recognised complication of any procedure entailing pleural manipulation, and is more likely to occur after the use of needles such as those used in acupuncture. Immediate radiography may not show collapse of the lung, which becomes evident only some hours later. In case 2, for example, collapse of the right lung was not shown radiographically until the day after admission.

These cases illustrate the danger of pneumothorax after acupuncture to the chest. The condition may take several hours to develop and may therefore not be radiographically evident immediately after the procedure. Patients in whom pleural trauma is suspected during acupuncture treatment should undergo repeat chest radiography after 24 hours to exclude pneumothorax.

We thank Dr I Peake for permission to report cases 1 and 3.

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(We suggest to readers that any suspected adverse reaction to a new drug should be reported to the Committee on Safety of Medicines, preferably on a yellow card. Serious or unusual reactions to all drugs should also be reported.)

SHORT REPORTS

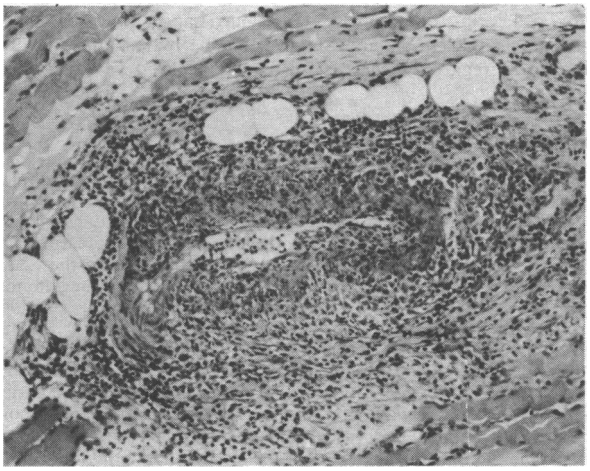
Relapsing polychondritis: relation to periarteritis nodosa

First described in 1923,[1] relapsing polychondritis is characterised by recurrent inflammation of cartilaginous structures and other tissues with a high concentration of glucosaminoglycans. Since Pearson *et al*[2] suggested the name relapsing polychondritis several cases have been reported detailing the ocular, audiovestibular, respiratory, and cardiac manifestations of the illness.[3 4] The disease may fall into the range of the systemic vasculitides, as recently suggested by Neild *et al*.[5] We report the evolution of a case with vascular lesions typical of periarteritis nodosa which preceded the characteristic features of relapsing polychondritis.

Case report

In May 1971 a 41-year-old woman was admitted to hospital with fever, arthralgia, and muscular pain. Since the winter of 1970 she had been treated with antibiotics for attacks of sinusitis and otitis. Her temperature was 38°C and her blood pressure 120/70 mm Hg. Her leg muscles were tender, and livido racemosa was present. Packed cell volume was 42% on admission, progressively decreasing to 23% six weeks later, when treatment was started. Leucocyte count was 12×10^9/l, mostly polymorphonuclear neutrophils. The erythrocyte sedimentation rate was 120 mm in the first hour. A test for antinuclear antibody was negative and rheumatoid tests were slightly positive. Australian antigen was not detected. The plasma urea concentration was 1·7 mmol/l (10·2 mg/100 ml) on admission, and creatinine 100 μmol/l (1·1 mg/100 ml). Signs of renal failure appeared during observation, with the plasma urea concentration at 16 mol/l (96 g/100 ml) and creatinine concentration at 600 μmol/l (6·8 mg/100 ml). Microscopical haematuria was detected, and proteinuria was less than 1·0 g/24 h. A muscle biopsy specimen showed a characteristic appearance of periarteritis nodosa (fig). Treatment with prednisolone 40 mg/day resulted in regression of clinical symptoms and restoration to normal of the blood picture and renal function within two months. A saddle-shaped deformity of the nose appearing at the end of 1971 suggested the diagnosis of relapsing polychondritis.

In December 1972 the patient developed an aortic diastolic murmur. Blood tests showed an erythrocyte sedimentation rate of 100 mm in the first hour and a leucocytosis of 12×10^9/l, predominantly composed of polymorphonuclear neutrophils. Fungal serological tests gave negative results. Cultures of transtracheal aspirate remained sterile for aspecific organisms, tubercle bacilli, and fungi. Several bronchial biopsies were performed after the appearance of excavated opacity in the apex of the right lung at the end of 1973 and showed normal bronchial mucosa, the chorion being infiltrated with polymorphonuclear leucocytes. Cartilage was present and partially replaced by fibrous tissue. The microscopical appearances, together with the clinical evolution and signs, confirmed the diagnosis of relapsing polychondritis. Antituberculous treatment was added to prednisolone (increased to 50 mg/day) despite negative culture results for tubercle bacilli. The cavitation in the apex of the right lung regressed progressively.



Muscle biopsy specimen. Small-sized artery showing extensive fibrinoid necrosis of its wall and surrounded by a heavy inflammatory infiltrate. (H and E. × 62.)

Comment

The diagnosis of relapsing polychondritis according to the criteriae of Dolan *et al*[4] was clearly established in our patient, whose symptoms and signs included conjunctivitis, joint pains, saddle-nose deformity, fever, raised erythrocyte sedimentation rate, and characteristic lesions of the bronchial cartilage. The aortic insufficiency further completed the clinical picture. Granulomatous disease of the lung as described in periarteritis nodosa and Wegener's granulomatosis was present in one case of relapsing polychondritis reported by Neild